Ultrasound-guided lymph node sampling in the initial management of breast cancer

C. Balu-Maestro, A. Ianessi, C. Chapellier, C. Marcotte, S. Stolear

Department of radiology, centre Antoine-Lacassagne, 33, avenue de Valombrose, 06189 Nice cedex 2, France

Abstract Ultrasound-guided fine needle sampling is proving very useful for avoiding surgical biopsy of the sentinel lymph node for N+ breast cancer. Because of its high specificity, cytology is sufficient in most cases. Focal or diffuse cortical thickening or the absence of the echogenic hilum irrespective of the size and shape of the lymph node are ultrasound signs which should be taken into account. The status of the lymph nodes in axillary and extra-axillary sites has an impact on the later management of patients and reduces the length of time for secondary lymph node dissection and adjuvant therapy, as one third of sentinel ganglion procedures can be avoided. It should be possible to optimise identification of the sentinel lymph node by the intradermal injection of ultrasound contrast agent. The cost/effectiveness ratio is positive but unknown and should be assessed in the initial management of breast cancer.

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With, as its objective, more accurate preoperative staging of breast tumours, fine needle lymph node sampling can be proposed for choosing between a sentinel lymph node procedure and wider dissection or neoadjuvant chemotherapy. We shall consider the value of lymph node ultrasonography and of guided sampling for the diagnosis of lymph node metastase and the impact of these techniques on therapeutic management.

Which lymph nodes should be sampled?

Clinical examination and mammography are insufficient for the diagnosis of lymph node metastase since their sensitivity is approximately 30% while their specificity is high at greater than 80%. As regards ultrasonography, the criteria are usually modification of the shape and ultrasound structure in B mode and modification of the vascularisation in colour Doppler mode [1]. The meta-analysis by Alvarez et al. [2], produced after

E-mail address: balu-maestro.catherine@nice.unicancer.fr (C. Balu-Maestro).

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reviewing 16 series, including 14 prospective studies published between 1986 and 2003, for which the gold standard was axial lymph node dissection in 11 studies and the sentinel lymph node procedure and/or wider dissection in the 5 others, found very variable values. The overall sensitivity of ultrasonography for palpable and non-palpable lymph nodes was between 66.1% and 72.7%, and the specificity between 44.1% and 97.9% based on the criteria of size (size greater than 5 mm or visible lymph node); based on morphological criteria (circular shape, cortical thickening, hypoechogenicity, lobulation, hilar filling), the sensitivity was 54.7% to 92.2% and the specificity between 80.4% to 97.1%.

If non-palpable nodes alone are considered, the greatest sensitivity was obtained based on size (73% in the lymph node dissection series and 60.9% in the series including both lymph node dissection and the sentinel lymph node procedure), while specificity was better when based on morphological criteria (from 92.4% to 96.5% respectively). In this meta-analysis, better sensitivity was found for non-palpable nodes with the size criterion (greater than 5 mm or visible lymph node) than with the morphological criteria, whereas whatever the clinical context, specificity was always greater when the morphological criteria were considered.

In the more recent series, since the meta-analysis by Alvarez et al. [2], totalling more than 600 patients [3—6], size is no longer considered to be a discriminating element and the threshold has been discussed. For Britton et al. [5], if the transverse axis is greater than 10 mm the hazard ratio is 7.4, whereas between 5 and 10 mm, it is only 2.7. Similarly, the shape classically defined by Solbiati et al.'s index [7] (long axis/transverse axis [L/T] less than 2 for a pathological lymph node) is not sufficiently discriminating. This needs to be lowered to 1.5 to obtain a useful specificity of 84.4% (versus 59% if L/T less than 2) to the detriment of sensitivity (45.9% versus 59%). At the present time, morphological alterations are more specific and occur earlier. For Esen et al. [3], the sensitivity of ultrasonography is 80% and specificity 94% if the morphological criteria are considered exclusively. The greatest predictive signs are the disappearance or the eccentric character of the hilum and the hypoechogenic character of the cortex. Normally, the hilum is twice as thick as the cortex, the thickness of which is considered as pathological when it is greater than 3 mm for concentric thickenings and greater than 2 mm for focal thickenings [5—8], aspects which are related to the invasion of the lymph node by afferent lymphatics (Figs. 1 and 2).

In order to increase the sensitivity of ultrasonography, certain authors puncture a normal lymph node or nodes, selecting the largest when the breast tumour is larger than 2 cm [9,10] or those closest to the tumour. In Doppler mode, only the existence of cortical vascularisation seems to have to be taken into account, and in combination with B mode the sensitivity is increased by 10% while the specificity is unchanged; quantitative criteria do not seem to have to be taken into account [3]. Colour Doppler is above all useful for visualising vascular landmarks during sampling procedures, but elastography is not reported in this application. Results have been published concerning the cervical nodes in ENT cancers.

False positives are seen as hypoechogenic hilar usually resulting from fatty involution (or more rarely by sinus histiocytes) or cortical follicular hyperplasia, and as small lymph nodes which are frequently round and hypoechogenic (Fig. 3). False negatives are represented by micrometastases. The value of ultrasonography increases with the risk, the number of lymph nodes invaded and the size of the metastasis (greater than 3 N+ and greater than 5 mm) [11]. Finally, a Taiwanese team have reported the usefulness of intraoperative ultrasonography for detecting non-sentinel metastatic lymph nodes [12,13], reducing the level of false

Figure 1. Lymphadenopathy. Focally-thickened cortex and amputation of the hilum although the shape is oval.

Figure 2. Focal thickening (0.37 mm).

Figure 3. The cortex is focally thickened and the hilum reduced. The biopsy is negative: ultrasound false positive.
negatives of the sentinel lymph node procedure (including after neoadjuvant chemotherapy) to less than 1.5% [12, 13].

What type of fine needle sampling?

Samples were of two types: cytological with 21, 22 or 23 gauge needles with or without aspiration, targeted on the cortex and multidirectional when the hilum was still present and, more rarely, microbiopsies (14, 16, 21 G trocars) (Fig. 4). The number of cytology samples was generally less or equal to 3, the products smeared on slides and usually centrifuged after being taken up in a CytoLiq solution. Certain authors used immunohistochemistry [14, 15] to increase the sensitivity of the cytology. As for microbiopsies, 2 to 5 cores were obtained with 14 to 21 G trocars, depending on the lesion size and vascular relations, often using a semi-automatic gun.

What were the results of the guided samples?

The results of Alvarez et al.’ meta-analysis [2] came from prospective studies using ultrasound-guided fine needle cytology (apart from one study concerning the results of microbiopsies [16] and a retrospective study [17]). If only the contributing cytological results are considered, the sensitivity varied between 43.5 and 94.9% and the specificity between 96.9 and 100%. When these results are added to those of the population initially selected, by considering patients for whom the ultrasound examination was negative and those whose samples were not contributive as false negatives, the sensitivity falls and varies between 30.6 to 62.9%. Heterogeneity in both cases disappears if the sentinel lymph node procedures are excluded that generate false negatives, but other biases are also involved — selection of different stages, surgical or radiological recruitment, different equipment — while the ultrasound sign criteria vary little. In five studies [14, 16—19] only suspect lymph nodes were punctured whereas in three studies, [20—22], all the lymph nodes were sampled regardless of their ultrasound appearance or their size. The sensitivity of fine needle cytology is lowered because the procedure requires ultrasound visualisation of the lymph nodes and for it to be technically possible; specificity is constantly excellent (approximately 100%), better than ultrasonography alone (80 to 96.5% depending on the morphological criteria for N0 patients. Few studies indicated the micro- or macrometastatic character of the false negatives. There were 10 studies later than the meta-analysis by Alvarez et al. (five retrospective [9, 10, 23—25] and five prospective [11, 15, 26—28] studies) published between 2005 and 2010, and for clinical N0 tumours they reported sensitivity of ultrasound-guided fine needle cytology of between 50 and 62% [10, 24, 25], apart from Baruah et al.’s series [28] in which the sensitivity was low (28%) but concerned two thirds of T1 classified lesions among the 502 patients in the series. One series [9] separated out the results of samples from normal lymph nodes and found sensitivity of 54% [10] with a false negative rate from the ultrasound examination of 13%, this result detected by fine needle cytology of these lymph nodes that exhibited no ultrasound abnormality and were not palpable. The heterogeneity of the results was seen to be related to the standard technique and the fall in sensitivity when non-contributory cytological products were included (1 to 15%) [9, 24, 25]. The results are significantly correlated:

- with tumour size (greater than 2 cm) with 35% sensitivity in T1 versus 67% in T2 in Somasundar et al.’s series [23], 56% in T1, 64% in T2, 82% in T3 and 100% in T4 in Koalliker’s series [9];
- with grades: for Baruah et al. [28], sensitivity was tripled for grade 3 compared with grade 1;
- with the number of N+: in Van Rijk et al.’s study [26] the number of N+ in the positive cytologies was 4.3 versus 2.2 in the negative cytologies for an identical number of lymph nodes excised (15). In Hinson et al.’s series [11], the sensitivity was 66% when there was one N+ and 100% when there were 3 N+;
- with the size of the metastasis: the false negatives were linked to micrometastases. In the Alkuwai and Auger study [25], sensitivity was 16% in the sentinel lymph node group where the mean size of the metastasis was 0.25 mm, whereas it was 88% in the lymph node dissection group where the mean size was 15 mm. Nevertheless, in most studies which have assessed this criterion, sensitivity was close to 100% above 5 mm. In three studies [11, 19, 29] in high risk patients, when the size of the metastasis was less than 5 mm and there was a single N+, all the cytologies were negative even if the ultrasound examination was abnormal;
- with the analysis technique: the best results (80%) were found in the series which used an immunohistochemical technique [14, 15].

As regards the microbiopsies, with an 18 G calibre in 1 to 3 cores, Duchesne [4] reported sensitivity of 94%, while Damera et al. [16] with 1 to 2 14 G cores only obtained 77%. These rates were lower in 2 recent series including normal lymph nodes, 53.4% for Britton et al. [5] and 69.1% for Garcia-Ortega [6]. In this series of 291 biopsies in 662 patients, 6.9% of N+ were found in the samples of lymph nodes which had a normal ultrasound appearance (lymph node dominating by size or the lowest in the axillary region). The false negatives were mainly found in normal lymph nodes and
in single cortical lesions [5]. Sensitivity increased with the grade and size of the tumour and the number and size of metastases but, despite the sampling technique used, there were 27.6% of false negatives when the size of the metastasis was between 5 and 10 mm [30]. Specificity was 100% for most of the studies. These results do not seem to lend support for the microbiopsy technique for lymph node samples, but it is easier to perform immunohistochemical techniques on such specimens. A small study has nevertheless compared 22 cytological samples with 27 microbiopsy samples of suspect lymph nodes and found a non-significant gain (of 7%) in sensitivity but double the financial cost [31]. All these data mean that this technique is not considered to be advantageous, at least, not as a first course of action. Sever et al. [32,33] recently reported the possibility of identifying the sentinel lymph node by periareolar injection of an echogenic contrast agent (0.2 to 0.5 mL × 3 of Sonovue®) compared with isotopic and colorimetric detection. By this method, the sentinel lymph node is correctly identified in 89% of cases as well as all the N+. Lymph node sampling could thus be correctly targeted on the sentinel lymph node by ultrasonography with intradermal injection.

What is the benefit?

The number of sentinel lymph node procedures avoided by lymph node sampling, redirecting patients to axillary lymph node dissection from the outset, was estimated for fine needle cytology in nine studies [6,10,15,23,24,26–29] and was between 8% [6] and 50% [3]. The rate of 28% in Baruah's series seems closer to what could be hoped for by performing fine needle cytology. For microbiopsies, Garcia-Ortega evaluated it as 33% [6]. Houssami et al.'s meta-analysis in 2011 concerning 31 studies estimated reconversion to lymph node dissection at 17.7% for intra-clinical lymph nodes characterised by fine needle cytology or biopsy [34]. Patients were redirected to neoadjuvant chemotherapy in 46% of the cytology cases [10], 23% of the positive biopsy cases [6] and 14% of T1 stages [23]. In Caroll et al.'s recent series [34], the sensitivity of lymph node ultrasonography associated with cytology and the size of the sentinel lymph node was 91%. The time before subsequent management was considerably reduced and before adjuvant treatment was reduced from 49 days to 23.3 days [35]. There is no direct evaluation of costs; the studies concerning management are partial or incomplete, are sometimes in the public and sometimes in the private sector. Reduction in cost was estimated in one study [29] as 20% for a reduction of 40% in recourse to the sentinel lymph node procedure. It is all the greater the higher the prevalence of N+.

Is there an indication for guided sampling before neoadjuvant treatment?

Few studies have evaluated this [12,13,23,25,36]. Ultrasound-guided fine needle cytology could replace the sentinel lymph node procedure before chemotherapy to distinguish truly N negative patients from those made negative by the chemotherapy, with the aim of choosing between sentinel lymph node and wider lymph node dissection during surgery. In Khan et al.'s series, 20 of 38 patients underwent fine needle cytology before chemotherapy [36]. After treatment, there was one false negative case/14 N+ cases in this group as against no false negatives for the eight N+ patients initially evaluated by the sentinel lymph node procedure.

Given its specificity, fine needle cytology, when positive, can also avoid the sentinel lymph node procedure for pretherapeutic staging. The results of the fine needle cytology of normal lymph nodes have not been made clear. A multicentre clinical trial is underway (GANEAZ) in which fine needle lymph node cytology is being performed where there is a suspect lymph node on the day of consultation for inclusion in the protocol. Intraoperative ultrasonography has also been studied in this indication, as mentioned earlier [12,13].

Is there an indication for guided sampling of parasternal lymph nodes?

The presence of parasternal lymph nodes stages the tumour as N2b or N3. All imaging techniques, CT, MRI, PET-CT and ultrasonography can visualise them. The factors predicting invasion of the parasternal lymph nodes are the existence of pericentral lymphadenopathies, a locally advanced tumour (rate of invasion of the parasternal chain: 28 to 52%), deep locations and central tumours. They mainly occur in the 1st and 2nd intercostal spaces. Irradiation of the parasternal chain is debated because of cardiac toxicity and a disputed impact on survival.

However, two large studies in 2008, reported by Veronesi et al. [37] and Zhang et al. [38], showed that irradiation had an impact on overall survival and local control. Veronesi’s study concerned 663 patients who underwent surgical biopsy of the parasternal lymph nodes (detected with a probe with or without scintigraphy) and, in the 10.3% of them that had been invaded the parasternal chain was irradiated. Five-year survival was greater than 95% and survival without recurrence was 78%. Zhang’s study concerned 809 clinical N2-3 patients: 112 parasternal lymph nodeopathies were detected by imaging (ultrasonography, CT, PET-CT) and in all the 10 cases of isolated parasternal involvement (average size = 13 mm) the ultrasound-guided biopsy was positive [38]. At 5 years, parasternal control was 89%, local control 80% and overall survival and survival without recurrence were 76% and 56% respectively. Are these data sufficient to suggest cytological checks on parasternal lymph nodes seen in imaging, particularly using ultrasonography?

In practice

Fine needle cytology of suspect lymph nodes defined by the ultrasound criteria described should be performed on a routine basis as soon as the sentinel lymph node procedure is envisaged. If a number of lymph nodes are suspect several sites may be selected, the choice depending essentially on the size and accessibility.
Conclusion

Ultrasound-guided fine needle cytology is a sensitive and, above all, very specific method. False negative are linked to problems of sampling often related to micrometastases or focal invasion less than 5 mm in size. This method should be optimised by puncturing the sentinel lymph node more precisely and in this context intradural injection of a contrast agent or elastography should be evaluated. With identification of lymph node metastases at the time of initial management of breast cancer the sentinel lymph node procedure can be avoided given the high predictive value of fine needle cytology. This is best performed at the same time as biopsy of the breast tumour to avoid inducing false positives (linked to an inflammatory reaction) both for the radiologist and pathologist. Microbiopsies do not seem to be essential as a first course of action. The benefits in terms of cost of such a strategy have not yet been analysed.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

References


